IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 077319/0371

Applicant: Raymond P. Warrell, Jr. *et al.*

Title: *PROCESS FOR PRODUCING ARSENIC TRIOXIDE FORMULATIONS AND METHODS FOR TREATING CANCER USING ARSENIC TRIOXIDE OR MELARSOPROL*

Serial No.: 10/425,785 Filing Date: April 30, 2003

Examiner: J. Goldberg Art Unit: 1614

DECLARATION UNDER 37 CFR §1.132

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

10 September 2003

Sir:

I, Ralph Ellison, state that:

1. I am a consultant to Cell Therapeutics, Inc. (CTI), the exclusive licensee of the application in caption ("the application"). CTI acquired its rights in the application through its purchase of PolaRx Biopharmaceuticals, Inc, a company that I co-founded and ran. While at PolaRx I was responsible for all aspects of clinical development of Trisenox® (intravenous arsenic trioxide). In my current capacity as consultant, I work closely with the Trisenox® (intravenous aresenic trioxide) clinical development team. I am familiar with the claims pending in the application.

2. I received my medical degree in 1986 from the University Of The Witwatersrand, in Johannesburg, South Africa. Before the application was filed, I was the head of the Company that developed Trisenox and worked closely with Dr. Ray Warrell, an inventor named in the application who at that time was a hired consultant to PolaRx. PolaRx sponsored the development in the United States of a protocol for treating acute promyelocytic leukemia (APL) via weight-based dosing of arsenic trioxide (ATO).

3. Dosage schemes for cancer treatment generally are quite different than those for the treatment of other diseases. Because cancer typically is caused by an abnormal proliferation of the

patient's own cells, for example, the targeting of disease tissue and cells will be non-specific and, hence, will have a detrimental effect on the patient's healthy tissue and cells. Consequently, toxicities that are unacceptable in the treatment of an allergic reaction, an infectious disease, and many other conditions are considered acceptable in the treatment of cancer, given the often deadly nature of latter condition. A decision to use a potentially toxic drug in cancer therapy is based, therefore, on a risk/benefit analysis.

4. The approach to determining a safe dose for most non-cancer disease types takes into account the size of the patient by weight, and this frequently gives rise to the use of a fixed or "flat" dose for a class of patients, such as all adult patients. This approach eases the calculation of the dosage amount during treatment. In the oncology field, on the other hand, the primary method for balancing the safety and the efficacy of a drug treatment entails metering dose by reference to the surface area of the patient.

5. For example, Smorenburg *et al.* states that, in "medicine, most drugs for adult patients are administered at a flat-fixed dose....In contrast, in oncology, the dosage of nearly all cytotoxic drugs is based on body-surface area (BSA) of the patient."[1] That is, instead of using a ratio of milligrams of drug per kilogram of patient, the standard approach in cancer treatment couches dosage in terms of milligrams of drug per square meter of patient surface area. This makes for a much more complex calculation of the actual amount to dose during treatment.

6. The prevalence of surface area dosing in cancer therapy is due in part to the potentially complex pharmacokinetics of weight based dosing between species, using conversion factors. By contrast, conventional wisdom in cancer therapy applies a conversion factor of one (1) in relation to surface area-dosing pharmacokinetics between species. See Voisin *et al.*[2] and Freireich *et al.*[3] This simplifies the assessment of a proposed safe dose in a field where the balance of efficacy to toxicity can be very problematic, and BSA dosing therefore has become the gold standard in oncology. As recently as 2001, Gurney notes that, "until there is a better method, BSA-dosing will prevail since there has

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[1] *J. Clin. Oncology*, 21:197-202 (2003).

[2] *Regulatory Toxicology and Pharmacology*, 12:107-116 (1990).

[3] *Cancer Chemotherapy Reports*, 50:219-244 (1966).

been over 40 years of experience with this method and 'old habits die hard.'"[4] Thus, even while debate continues on current, BSA-based dose calculations for chemotherapy, oncologists principally employ BSA dosing to balance toxicity and efficacy based on patient size.

7. Those working in the oncology field sometimes consider flat dosing as an alternative to BSA dosing. For example, Westervelt *et al.* explored the adjusting of a flat dose of arsenic trioxide for a single APL patient.[5] In their 1997 abstract, Westervelt *et al.* flat-dosed the patient 10 mg of arsenic trioxide daily. In view of a resultant and profound leukocytosis, as well as other parameters indicating lack of efficaciousness, Westervelt *et al.* increased the dose to 50 mg/day. Having observed significant toxicity during and after the treatment, they concluded that toxicities had to be considered when dosing arsenic trioxide.[6]

8. In the course of developing a clinical protocol for treatment of APL with ATO, the present inventors also initially adopted a flat-dosing approach and, with their first five patients, used a daily 10-mg dose.[7] Patient 5 in the initial group relapsed within 24 days of achieving total remission and before completion of the consolidation therapy. As the patient was a very large individual (163 kg), the inventors questioned whether he might have received too little drug at a flat dose of 10 mg daily. The relevant literature did not suggest this problem, since there was no teaching that the size of a patient should be considered in arriving at an appropriate dosage.

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[4] *Brit. J. Cancer*, 86:1297-1302 (2001).

[5] Abstract 3859, *Blood*, 90 (Suppl. 1): 249b (1997)

[6] Westervelt *et al.* also back-calculated the administered flat doses, identifying them in weight-based terms, too. Thus, the initial 10 mg/day dose was translated to 0.08 mg/kg, and 50 mg/day dose to 0.40 mg/kg. *Id.* The fact that flat dosing was used for this initial patient is confirmed in a later article by Zhang *et al*, which again references "10 mg daily" and "50 mg daily" for this same patient, while characterizing the protocol for 4 subsequently-treated patients as being one "with the dosage based on actual body weight." In both the abstract and in this later study, it is suggested that full Phase I/II studies would be needed to determine a proper dosing level for a broad population. See Zhang *et al.*, *Modern Pathology*, 13:954-61 (2000). Another later study, reported by Westervelt *et al.*, *Blood*, 98:266-71 (2001), did undertake a dose escalation study in order to determine an appropriate dosage. Only Phase I has been reported, and no dose escalation beyond the initial dose of 0.1 mg/kg per day was undertaken, possibly because of the "2 unexpected deaths" among the first nine patients. Thus, the Phase I trial failed to determine a proper dosing level, and leaves open the question of whether a dose that results in both efficacy and acceptable toxicity can be achieved for this drug.

[7] The flat dosing was in accordance with earlier reports illustrated by Westervelt *et al.* (1997), *supra*, Shen *et al.*, *Blood*, 89:3354-3360 (1997), and Zhang *et al.*, *Chinese J. of Hematology*, 17(2) (1996).

9. Since the drug had been well tolerated by the initial patients, and in order to avoid the possibility of under dosing, as was believed to have occurred with Patient 5, the dose was increased to a 15 mg flat dose for all subsequent patients.. This dosage amount was given to Patients 6 and 7. Patient 8 was a 13 year-old girl and of smaller stature, however. For this patient, therefore, the inventors chose to revert to the original, 10 mg-daily dosage, as a precaution against the possibility of overdosing. Patient 9 was a 9 year-old boy and, because of his size, was given a flat dose of only 5 mg daily. Patient 10 was given the newer dosage of 15 mg daily.

10. Upon reviewing the results for the first ten patients, the inventors concluded that the standard flat dosing method, per Shen and Zhang, appeared not to be efficacious for large people and was too toxic for small people. They further concluded that their initial approach of adjusting the flat dose was arbitrary and did not allow for a balancing of toxicity and efficacy in a treatment protocol to be used across a broad population of patients. Prior to treating Patient 11, therefore, the inventors decided to implement a technique other than flat dosing. Rather than turning to standard BSA dosing, the technique widely used by oncologists for dosing of chemotherapeutic drugs, the inventors chose to attempt to develop a weight-based dosing scheme. Employing data generated from the first ten patients, the inventors calculated a putative weight-based dose of 0.15 mg/kg daily. This dose was used for the next two patients and was ultimately chosen to complete the study and to conduct the pivotal phase III trial in which 40 patients participated. The results of this trial are reported in Soignet *et al.*, *J. Clin. Oncology*, 19:3852-3860, and showed that arsenic trioxide treatment is both safe and effective. Eighty-five percent of patients achieved clinical complete remission, and there were no treatment-related deaths.[8] Westervelt *et al.* contrasts the results achieved in the trial reported in Soignet *et al.* with the unexplained deaths in their study, noting that "in another series of 40 APL patients treated with 0.15 mg/kg per day arsenic trioxide for variable periods, no life-threatening arrhythmias or treatment-related deaths were reported."[9] While proffering various theories to explain the differing results, Westervelt *et al.* reached no conclusion on this point.

11. The results obtained in the trial reported in Soignet *et al.* led to approval by the FDA of arsenic trioxide (Trisenox). Subsequent to FDA approval of Trisenox , data on an additional 2,228

[8] Soignet *et al.* (2001), page 3854 ("clinical efficacy") and page 3856 ("adverse events").

[9] Westervelt *et al.*.(2001), page 270.

patients (treated at doses of about 0.15 mg/kg per day or greater) have been collected, via post marketing surveillance, and in clinical trials. To date no deaths attributed to arsenic associated arrhythmia have been reported, providing further evidence that treatment with arsenic trioxide is safe.

12. Subsequent to the present invention, another group of oncologists chose to modify flat dosing to a dosing based upon the patient's size; this, in recognition of a need to protect patients from toxic doses of ATO during the APL treatment. See Au *et al.*, *Annals of Oncology*, 14:752-57 (2003). Au *et al.* adopted a BSA dosing scheme, however. Thus, they described the use of BSA dosing in the context of treating a group of patient with relapsed APL. Initial treatment was on a flat-dosage basis for APL patients who underwent bone-marrow transplantation and ATO therapy. For double-relapse patients, however, the dosage was metered to take into account the size of the patient on a surface area basis. The difference in initial dosing and double-relapse dosing can only be interpreted as an acknowledgement of the need to balance toxicity and efficacy for the patients who had been weakened by extensive therapy beforehand. When faced with the same problem that the present inventors confronted, in other words, Au *et al.* resorted to more conventional treatment scheme, with dosing based upon patient surface area.

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I hereby declare that all the statements made herein of my known knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Sept 11 2003
Date

Ralph Ellison